IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Neil H. Bander
Serial No. : 09/357,709
Filed : July 20, 1999
Title : TREATMENT AND DIAGNOSIS OF PROSTATE CANCER

Art Unit : 1642
Examiner : Gary B. Nickol

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL

Appellant is appealing the final rejection of claims 68-77, 79-81, 107, 111, 116-128 and 130-152 dated November 3, 2004. A Notice of Appeal was mailed on December 8, 2004.

(1) Real Party in Interest

The Real Party in Interest is Millennium Pharmaceuticals, Inc., 40 Landsdowne Street, Cambridge, Massachusetts 02139. Millennium Pharmaceuticals, Inc. is the exclusive licensee of the above-identified application from the assignee, Cornell Research Foundation.

(2) Related Appeals and Interferences

The present appeal is related to appeals filed, or soon-to-be filed (in the case of 09/929,665), in the following copending applications:

USSN 09/357,710;
USSN 09/357,704;
USSN 09/929,546; and
USSN 09/929,665.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

2/15/05
Date of Deposit

Alissa Passacantilli
Signature

Alissa Passacantilli
Typed or Printed Name of Person Signing Certificate

(3) Status of Claims

Claims 68-77, 79-81, 107, 111, 116-128 and 130-152 are pending.

Claims 68-77, 79-81, 107, 111, 116-128 and 130-152 are rejected under 35 U.S.C. § 112, first paragraph.

Claims 68-77, 79-81, 107, 111, 116-128 and 130-152 are being appealed.

(4) Status of Amendments

All of the amendments filed in this case have been entered.

(5) Summary of Claimed Subject Matter

One aspect of the claimed invention features a method of detecting normal, benign hyperplastic, or cancerous prostate cells in a human subject. The method comprises: providing an antibody or antigen binding portion thereof which competes for binding to prostate specific membrane antigen (PSMA) with a monoclonal antibody selected from the group consisting of an E99, a J415, a J533, and a J591 monoclonal antibody, wherein the antibody or antigen binding portion thereof is bound to a label effective to permit detection of normal, benign hyperplastic, or cancerous prostate cells; administering the antibody or antigen binding portion thereof to the human subject; and detecting the presence of the normal, benign hyperplastic, or cancerous prostate cells by detecting the label. Support can be found, e.g., at page 10, line 17 through page 11, line 8; page 14, line 19 through page 15, line 10; and page 27, line 26 through page 28, line 6.

In another aspect, the claimed invention features a method of detecting benign hyperplastic prostate cells in a human subject, that comprises: providing an antibody or antigen binding portion thereof which competes for binding to prostate specific membrane antigen (PSMA) with a monoclonal antibody selected from the group consisting of an E99, a J415, a J533, and a J591 monoclonal antibody, wherein the antibody or antigen binding portion thereof is bound to a label effective to permit detection of benign hyperplastic prostate cells; administering the antibody or antigen binding portion thereof to the human subject; and detecting the presence of the benign hyperplastic prostate cells by detecting the label. Support

can be found, e.g., at page 10, line 17 through page 11, line 8; page 14, line 19 through page 15, line 10; and page 27, line 26 through page 28, line 6.

Another aspect of the claimed invention features a method of detecting cancerous prostate cells in a human subject, that comprises: providing an antibody or antigen binding portion thereof which competes for binding to prostate specific membrane antigen (PSMA) with a monoclonal antibody selected from the group consisting of an E99, a J415, a J533, and a J591 monoclonal antibody, wherein the antibody or antigen binding portion thereof is bound to a label effective to permit detection of cancerous prostate cells; administering the antibody or antigen binding portion thereof to the human subject; and detecting the presence of the cancerous prostate cells by detecting the label. Support can be found, e.g., at page 10, line 17 through page 11, line 8; page 14, line 19 through page 15, line 10; and page 27, line 26 through page 28, line 6.

(6) Grounds of Rejection

Claims 68-77, 79-81, 107, 111, 116-128 and 130-152 stand rejected under 35 U.S.C. §112, first paragraph "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the invention."

(7) Argument

Claims 68-77, 79-81, 107, 111, 116-128, and 130-152 stand rejected under 35 U.S.C. §112, first paragraph, "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the invention." Specifically, the Examiner asserts that "'competes for binding' finds no support in the original claims and or disclosure as filed." Thus, the sole issue is whether the specification and claims as filed provide written description support for the "competes for binding" element of the claim term "competes for binding to prostate specific membrane antigen with a monoclonal antibody selected from the group consisting of an E99, a J415, a J533, and a J591 monoclonal antibody." This phrase is

often referred to herein as the "disputed claim term." No other element of the claim was said to lack written description.

Appellant respectfully traverses the rejection.

The case law sets forth at least three ways that written description support for claimed subject matter can be shown. These are *in haec verba* support, explicit support and inherent (or implicit) support. *In haec verba* and explicit support are often referred to as forms of express support. *In haec verba* support comes from language in the specification that identically recites the claimed subject matter. Explicit support is derived from language that while not identical to the language in the claim, is equivalent thereto. Lastly, where express language is lacking, support may be found either inherently (or implicitly) in the specification. See, e.g., MPEP 2163(I) and MPEP 2163 (II)(A)(b).

As provided in the response filed on August 13, 2004 and the Declaration of Abbie Celniker under 37 CFR § 1.132 filed on August 13, 2004[1], and as set forth below, the instant application provides explicit written description support for the disputed claim term. This is not a situation were support needs to be implied from the disclosure of a genus and/or species. Therefore, there is no need to rely on case law regarding implicit support. However, even if it is argued that there is no explicit support (which is not the case), the specification provides inherent or implied written description support for the disputed claim term.

Before proceeding further Appellant points to the Declaration, which supports the arguments made herein. The Declaration shows that Dr. Celniker reviewed the specification and found that one of ordinary skill in the art, at the time of filing, would have found that the inventor was in possession of the disputed claim term. She concluded as follows in the Declaration:

> 8. I want to be clear that I am not saying merely that the text makes it obvious to arrive at "antibodies or portions thereof that compete for binding to PSMA with monoclonal antibodies E99, J415, J533 and J591" or that the specification discloses a general concept of what antibodies might compete and that it is only obvious that these would be E99, J415, J533 and J591. On the contrary, it is clear to me that, upon reviewing the specification of the above-referenced application, one of ordinary skill in

[1] Hereinafter referred to as "the Declaration", a copy is submitted herewith in the Evidence Appendix.

> the art at the time the application was filed would have believed the text itself describes and actually shows possession of the subject matter in question. It is really a rather simple matter: a series of consecutive sentences in the specification build on one another and require this conclusion.

We continue now with Appellant's arguments.

The specification provides explicit support for the disputed claim term

The written description requirement is met if the specification shows that an applicant was in possession of the claimed invention at the time of filing. "When the original specification accomplishes [this], regardless of *how* it accomplishes it, the essential goal of the description requirement is realized." *In re Smith*, 481 F.2d 910, 914, 178 USPQ 620 (CCPA 1973). It is well accepted that "in order to satisfy the written description requirement, the disclosure as originally filed does not have to provide *ad haec verba* support for the claimed subject matter at issue." *Purdue Pharma v. Faulding, Inc.*, 230 F.3d 1320, 56 USPQ 2d 1481 (Fed. Cir. 2000); and MPEP § 2163.02. As provided, for example, in *In re Wright*, 866 F.2d 422, 9 USPQ2d 1649 (Fed. Cir. 1989), "the fact...that the exact words here in question...are not in the specification is not important." See also MPEP 2163.02, which provides: "The subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement."

The rejection is based on a combination of a misunderstanding and misapplication of the law and a misinterpretation of the text of the specification. The analysis in the Final Office Action[2] begins with the following statement:

> Applicants further refer to several court decisions: ***in Re Smith, Purdue Pharma v. Faulding, Inc., and In re Wright*** which taken out of context, appear to conclude that the original disclosure need not provide literal support or exact wording for claimed subject matter. (italics and bold typeface in the original, underlining added)

One must conclude from the quoted text that the rejection is based, at least in part, on the view that the case law requires "literal support or exact wording for claimed subject matter" and

[2] See pages 2 and 3, of the Final Office Action of November 3, 2004

that only by taking the cases "out of context" can one come to the conclusion that literal or exact support is not required. This is incorrect, see, e.g., MPEP 2163 (I)(B) which provides, "While there is no *in haec verba* requirement, newly added claim language must be supported in the specification through express, implicit, or inherent disclosure." See also, MPEP 2163.02, which provides, "The subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement." While this is certainly not the only flaw in the analysis of the Final Office Action, this misunderstanding, i.e., that express support must be literal or exact (i.e., *in haec verba*), permeates the analysis and is one of the factors that contributes to the erroneous conclusion that the specification lacks written description for the disputed claim term.

The Final Office Action continues as follows:[3]

> As set forth previously, the specification only provides a written description and indicates possession of a genus of antibodies that bind to the extracellular domain of PSMA and four such monoclonal antibodies, or *species* of the genus, e.g. E99, J591, J415, or J533.
>
> The rejected claims, (i.e. those covering a class of antibodies that "compete for binding" to E99, J591, or J533) are not representative of the above genus or species. In particular, competing antibodies represent those antibodies that have yet to be discovered and that comprise the same binding properties as E99, J591, J415, or J533.

In the last sentence, the analysis confuses discovery of an actual antibody with a very different concept, that of possession of the invention (which is not a specific physical antibody but rather a legal construct). Again, the law is misstated or misapplied—the analysis is based on the wrong standard for what must be possessed by the inventor. In addition, the analysis includes a factual error; antibodies that compete with three of the species have been identified--the specification provides that J591, J533, and E99 compete with one another.[4] The comments in the Final Office Action on whether the disputed claim term is representative may be referring to the issue of whether the specification contains implicit support for the disputed claim term. Appellant's position is that there is very clear explicit support for the disputed claim term and

---

[3] See page 3,second and third paragraphs, of the Final Office Action of November 3, 2004
[4] See page 28, lines, 1-3, of the specification.

that the issue of implicit support for the disputed claim term need not be reached. Nevertheless, the question of implicit support is dealt with in a separate section below.

The analysis in the Final Office Action turns next to a passage in the specification which concerns the use of competing and non-competing antibodies in the preparation of prodrug/activator systems.[5] Most, if not all, of the analysis in the Final Office Action concerns this passage. Appellant will first discuss the relevance of the passage to written description of the disputed claim term and then go on to discuss the analysis of the passage found in the Final Office Action.

The specification as a whole is directed to anti-PSMA antibodies, to methods of making such antibodies, and to a variety of uses to which such antibodies can be put. One disclosed use of antibodies of the disclosure is as starting materials for use in the construction of antibody-prodrug conjugates and antibody-prodrug activator conjugates. Two classes of antibodies of the invention, competing and non-competing, are described in the section on the selection of antibodies as starting materials for use in making the conjugates .[6] The passage referred to above provides as follows:

> a first biological agent[7] is conjugated with a prodrug which is activated only when in close proximity with a prodrug activator. The prodrug activator is conjugated with a second biological agent <u>according to the invention</u>, preferably one which binds to a non-competing site on the prostate specific membrane antigen molecule. Whether two biological agents bind to competing or non-competing binding sites can be determined by conventional competitive binding assays. (emphasis added)

Thus, the passage, alone or in combination with the rest of the specification, explicitly discloses two types of antibodies:

1. Antibodies that compete for binding with an antibody according to the invention; and

---

[5] See page 27, lines 27-35, of the specification.
[6] See page 27, lines 27-35, of the specification.
[7] Biological agent are discussed as follows at page 13, lines 14-19, "The process involves providing a biological agent, such as an antibody or binding portion thereof, probe, or ligand, which binds to an extracellular domain of prostate specific membrane antigen of (i.e., a portion of prostate specific membrane antigen which is external to) such cells."

2. Antibodies that do not compete for binding with an antibody according to the invention.

The passage also provides that non-competing antibodies are preferred in one embodiment and that non-competing antibodies should, in that embodiment, be distinguished from competing antibodies. The text also provides, see, e.g., the last sentence of the quoted passage, what constitutes a competing biological agent and a non-competing biological agent by stating that "whether two biological agents bind to competing or non-competing sites can be determined by conventional competition binding assays." So, whether preferred or not for use in this particular application (prodrug/prodrug activator systems), it is clear the text explicitly describes antibodies which compete with an antibody of the invention. The effort the inventor went to in order to characterize the two different classes of antibodies, and the very recognition of the necessity of avoiding the competing class in a preferred conjugate construct, shows that the inventor was in possession of the concept of competing antibodies. Thus, a person of ordinary skill in the art at the time the application was filed could reasonably conclude that the inventor was in possession of the concept of having "an antibody that competes for binding with an antibody according to the invention."

All that remains is to show support for the concept that the antibody "according to the invention" referred to in the cited language above can be one of the antibodies recited in the claims, namely E99, J415, J591 or J533. Antibodies E99, J415, J533 and J591 are disclosed throughout the specification as being antibodies of the invention. They are the only species described in the specification. In fact, the very next sentence[8] after the passage recited above is as follows:

> For example, monoclonal antibodies J591, J533, and E99 bind to competing binding sites on the prostate specific membrane antigen molecule. Monoclonal antibody J415, on the other hand, binds to a binding site which is non-competing with the site to which J591, J533, and E99 bind.

Upon reviewing the specification one of ordinary skill at the time the application was filed, could have reasonably concluded that monoclonal antibodies E99, J415, J533 and J591 are "antibodies according to the invention."

---

[8] See page 28, lines 1-6, of the specification.

Given that the specification clearly supports the concept of "antibodies that compete for binding with an antibody of the invention," and that J415, J591, J533 and E99 are each antibodies of the invention, a skilled artisan could reasonably conclude that that the inventor was in possession of the disputed claim term, namely "competes for binding to prostate specific membrane antigen with a monoclonal antibody selected from the group consisting of an E99, a J415, a J533, and a J591 monoclonal antibody" at the time of filing. In addition to the arguments presented herein, attention is directed to the Declaration. It provides that one of ordinary skill in the art at the time the application was filed would have found that the specification discloses and that inventor was in possession of the disputed claim term.

We turn now to the analysis in the Final Office Action of the passage discussed above. The analysis does the following:

it improperly ignores the plain language of the passage which explicitly describes antibodies which compete with an antibody of the invention;

it takes the incorrect position that the cited passage must be read in isolation from the rest of the specification and that the cited passage only provides written description for antibodies which can be used in prodrug/activator systems and that to do otherwise is to take the support "out of context";

it incorrectly takes the position that competing antibodies will not work in such systems;

it is based, at least in part, on misinterpretation of the law, namely that there can only be written description for antibodies that work in prodrug/activator systems; and

it comes to the erroneous conclusion that there is no written description support for the disputed claim term. If any element of this argument fails the entire argument falls. In fact, as set out below, each of the elements of this analysis is fatally flawed.

The analysis in the Final Office Action begins by ignoring both the specification as a whole, which is very largely devoted to anti-PSMA antibodies, and the plain language of the cited passage.

The analysis then goes on to erect an intricate analytical framework, by first arguing that the support for the disputed claim term has been taken out of context in the Appellant's

arguments. In response to the Appellant's remarks about the passage[9] discussed earlier herein the Final Office Action provides the following argument:[10]

> This argument has been considered but is not found persuasive, as it appears that the alleged support has been taken out of context. The passage that applicants refer to pertains to biological agents conjugated to prodrugs- such as antibody conjugates.

The Final Office Action argues that the passage relates only to antibodies which are conjugated to the prodrug or activator (see the emphasis on the word conjugated). It may be that this stems from the view that express support must be *in haec verba* support, see the section on the discussion of the law on pages 5 and 6 above. A review of the specification as a whole, and of the cited passage, shows that this interpretation of the passage is far too restrictive. The entire specification is directed to anti-PSMA antibodies and to methods of making such antibodies, and to a variety of uses to which such antibodies can be put. As discussed above, the cited passage describes particular classes of antibodies of the invention, competing and non-competing, in connection with selecting starting materials for use in making the conjugates. There is simply no support in the specification for the position that the classes of competing and non-competing antibodies have no existence outside the use in a prodrug/activator conjugate. The two classes of antibody exist independently of the prodrug system.

The analysis in the Final Office Action goes on as follows:[11]

> In the instant case that conjugated prodrug becomes activated "only when in close proximity with the prodrug activator". Thus, the fact that a preferred embodiment of a prodrug/prodrug activator scenario is one in which the biological agent binds in close proximity to one another (i.e...to non-competing sites) on the antigen is not surprising given the fact that said activators must be nearby to activate the prodrug. In contrast, however, it would be surprising and quite complex to conceive of administering biological agents conjugated to prodrugs and or prodrug activators that bind competing sites on the antigen because such sites are indicative of the same epitope. Hence the administration of biological agents (for the purposes of activating a prodrug) that bind to competing sites would effectively reduce the probability that a prodrug would be activated. Thus, applicants alleged support for the inclusion of "competing" sites is not

[9] Reproduced on page 7 herein and found at page 27, lines 27-35, of the specification.
[10] See page 3, last paragraph, of the Final Office Action of November 3, 2004.
[11] See pages 3 and 4 of the Final Office Action of November 3, 2004.

found persuasive because there is no contextual nexus that adequately provides support for the newly amended claims.

In this section, the analysis argues that competing antibodies will not work in a prodrug/activator system, that only antibodies that work in a conjugate have written description, and therefore there is no written description of competing antibodies. The reasoning is based on a misinterpretation of the specification, on factual error or unfounded speculation, and on misapplication of the law.

First, the passage is misinterpreted. It does not limit prodrug/activator systems to those using non-competing antibodies. The passage on antibody selection for prodrug applications merely says that non-competing antibodies are preferred—it by no means rules out the use of competing antibodies. The inventor could have used more restrictive language, e.g., he might have said "competing antibodies are not suitable for use in prodrug/activator systems" but he did not do so.

Furthermore, the analysis is based on unfounded assumptions or factual error about the prodrug/activator system. No reasonable basis is presented to support the view that despite the plain language in the cited passage, a competing antibody would not work in a prodrug/activator system. The passage discloses the need for close proximity of the prodrug and activator. The Final Office Action argues that the recited close proximity is equivalent to non-competing sites (see the language in the Final Office Action that reads as follows, "close proximity to one another (i.e...to non-competing sites[12])." There is nothing in the application or of record, other than the speculation or unsubstantiated conclusion in the Final Office Action, that suggests that an antibody would have to bind a non-competing site on an antigen to be "in close proximity." E.g., competing antibodies that bind to overlapping epitopes, in the process of competing one another off and on the antigen, might just as well create the needed close proximity between the prodrug coupled to one of the competing antibodies and the activator coupled to another competing antibody. A prodrug activator conjugate might just as well activate a prodrug conjugate by binding an epitope on a first PSMA antigen located "in close proximity" to a

[12] See the second sentence of the language from the Final Office Action reproduced at page 10 above.

second PSMA antigen that is bound by the prodrug conjugate at the same epitope on the second PSMA antigen (PSMA is found as a dimer on cells).

Finally, the rejection is based on a misapplication of the law. The analysis in the Final Office Action relies heavily on the argument that prodrug/activator systems made with competing antibodies will not work. See the text of the arguments quoted above, especially the segment which reads as follows, "... it would be surprising and quite complex to conceive of administering biological agents conjugated to prodrugs and or prodrug activators that bind competing sites on the antigen because such sites are indicative of the same epitope." The analysis confuses the utility or enablement of a prodrug/activator system (which is not the subject of the claims) with written description of the antibody components used to make the prodrug/activator system. The analysis assumes that a prodrug/activator system which uses competing antibodies will not work or could not be made to work without undue experimentation. Even if that were true, it would go to the issue of whether claims to a prodrug/activator system made with competing antibodies would have utility or would be enabled, and not to the issue of whether there is written description for the antibodies used to make the conjugate. [13]

Thus, the argument in the Final Office Action is flawed at every stage. To summarize:

First, it ignores the plain language of the cited passage which explicitly describes competing antibodies. Quite simply, the passage provides explicit support for competing antibodies so the argument in the Final office Action falls once one looks to this language. The analysis is wrong and as such the rest of the arguments are moot.

Next, without any support, it is concluded that the classes of antibody explicitly described must be interpreted as having an existence only in relationship to prodrug/activator systems. There is absolutely no basis for this. The analysis is wrong and as such the rest of the arguments, which depend on this, are moot.

Next, the analysis argues that competing antibodies will not work in such systems. This is based on a misreading of the passage and unwarranted assumptions or factual error with regard to the types of antibodies which can be used in the conjugates.

---

[13] This is not Appellant's position. Appellant does not take the position that any particular prodrug/activator system lacks utility or is not enabled.

Finally, the analysis argues that there can only be written description for antibodies that work in prodrug/activator systems. Here the analysis confuses utility or enablement of conjugates with written description of the antibodies. Even if the arguments were right about the enablement or utility of the conjugate, it would not defeat written description of the antibodies.

Perhaps the most important flaw in the arguments in the Final Office Action is that they never addresses the issue of why there is no express support for the disputed term, despite the plain explicit language in the specification. Instead, the analysis centers on an intricate multistage analysis that is irrelevant and/or flawed at every stage. The PTO has not met the burden of showing that the written description of the claims is lacking.

The Final Office Action then provides further discussion of mechanism of binding and the fact that the passage prefers non-competing antibodies.[14] This is simply more of what Appellant has addressed above. It is irrelevant and flawed for the same reasons.

The arguments in the Final Office Action conclude as follows:[15]

> Thus, there is never a suggestion or a contemplation to possess or use antibodies that recognize the same epitope or compete with E99, J415, J533, and J591. Thus, the applicant's arguments have not been found persuasive and the rejection is maintained. (emphasis in original)

Again, the analysis ignores the plain language of the passage discussed in detail above. The refusal to recognize this may come at least in part from the view that express support must be *in haec verba* support, see the section on the discussion of the law on pages 5 and 6 above. Whatever the reason, the analysis ignores the plain language, and relies on arguments that are irrelevant and/or flawed at every stage to thereby come to the conclusion that there is no express support. Appellant turns now to the issue of implicit support.

The specification provides implicit support for the disputed claim term

Even if it is argued that there is no explicit support for the disputed claim term, there is implicit written description support for it. The MPEP and the case law allow for inferring a sub-

[14] See page 4 of the Final Office Action of November 3, 2004.
[15] See page 4 of the Final Office Action of November 3, 2004.

genus from other disclosure when the facts support doing so. *In re Smith,* 458, F.2d 1389, 173 USPQ 679 (CCPA 1972), provides that "precisely how close the description must come to comply with section 112 must be left to case-by-case development ... it cannot be said that a sub-genus is necessarily always implicitly described by a genus encompassing it and a species upon which it reads." *In re Smith(1972)* does not enunciate a hard and fast rule that a genus and/or species cannot support a sub-genus. Instead, the determination must be made on a case-by-case basis. See, e.g., MPEP 2163(II)(A)(3)(b), which, citing *In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, provides:

> "[W]here no explicit description of a generic invention is to be found in the specification mention of representative compounds may provide an implicit description upon which to base generic claim language".

MPEP 2163.05 (II) refers to two cases which dealt with finding support for a sub-genus from generic and species disclosure, *In re Lukach,* 442 F. 2d 967, 169 USPQ 795 (CCPA 1971) and *Ex parte Sorenson*, 3 USPQ2d 1462 (Bd. Pat. App. & Interf. 1987).

In *In re Lukach*, the applicant argued that it was entitled to a sub-generic claim to a specific (narrow) range of molecular weight, namely 2.0-2.6. The applicant reasoned that because the disclosure included a broader genus range and a single species which inherently fell into the specific narrower sub-generic range (the sole species had a molecular weight of 2.6), it should be allowed to narrow the generic claim to the narrower specific sub-generic range. The applicant, relying largely on *In re Risse*, 378 F.2d 948, 154 USPQ 1 (1967) (which was at least partially overturned later), argued that support for a sub-genus required nothing more than the disclosure of a broader genus which wholly encompasses the questioned sub-genus and disclosure of a single species within the new sub-genus. The court found that even if the applicant's reliance on *In re Risse* was appropriate, there was no disclosure of the broader genus range. The court reasoned that a single species example of 2.6, alone, with nothing else in the specification or art pointing to the range, would not support a range of 2.0-2.6.

In *Ex parte Sorenson,* the original application disclosed a broad genus of "copper complexes of carboxylic acids" as well as a number of species. Five working examples were

from the originally unclaimed sub-genus of "binuclear copper complexes of carboxylic acids." Four of these working examples were from the sub-sub-genus of "binuclear copper complexes of aryl carboxylic acids" and one was from the sub-sub-genus of "binuclear copper complexes of alkyl carboxylic acids." The applicant sought to add a claim to the sub-genus, as well as to the two sub-subgenera. The examiner rejected the added sub-generic and sub-sub-generic claims for lack of implicit written description. The Board, reversed, relying in part on *In re Kalsow*, 707 F.2d 1366, 217 USPQ 1089 (Fed. Cir. 1983), for the proposition that the test is whether the originally filed specification reasonably conveys to a person of ordinary skill that the applicant had possession of the subject matter.

The instant case, when viewed from the perspective of implicit support, concerns the sufficiency of the written description of a sub-genus—"an antibody (or binding fragment) which competes with one of J591, E99, J415 and J533." This is referred to below as the "disputed sub-genus." One important consideration in *In re Lukach* and *Ex parte Sorenson* was the whether there was disclosure of a broader genus and a disclosure of species which would fall under the disputed sub-genus. Another critical consideration in analyzing the specification for support was whether anything in the specification pointed to the questioned sub-genus. Therefore, Appellant begins the analysis with a review of such disclosure in the specification.

The specification discloses the following genus, sub-genera (the disputed sub-genus is shown in brackets), and species, arranged in order of descending scope:

- A broad genus of all antibodies that bind to the extracellular domain of PSMA.[16] The Examiner has admitted that the specification describes this genus.[17]
- A relatively broad sub-genus of competing antibodies, i.e., all competing antibodies, which is broader than the disputed sub-genus.[18]
- [Antibodies that compete with J591, E99, J415 and J533]
- A relatively narrow sub-genus of competing antibodies, i.e., the sub-genus of J591, E99, and J533, which is narrower than the disputed sub-genus.[19]

---

[16] See page 16, lines 22-27, of the specification.
[17] See page 3, first full paragraph, of the Final Office Action of November 3, 2004.
[18] See page 27, lines 27-35, of the specification.

• Four species J591, E99, J415 and J533.[20] The Examiner has admitted that the specification describes these species.[21] These species fall within the broad genus and the relatively broad sub-genus of competing antibodies. Several of them fall within the relatively narrow sub-genus of competing antibodies. They all fall within the disputed sub-genus of competing antibodies.[22] They are fully representative of the genus. The species share structural and functional homology but are representative of the sub-genus, some compete with one another while one does not.

Thus, the disputed sub-genus is bracketed by explicit disclosure in the specification. The broad genus, and the relatively broad sub-genus of competing antibodies, are broader than the disputed sub-genus. The relatively narrow sub-genus of competing antibodies, and the species, are narrower than the disputed sub-genus. In this respect, namely the presence of a broader taxa, the facts in the instant case are far more like those in *Ex parte Sorenson*, where support was found. The facts are even stronger here, as there are two broader genera, the genus and the relatively broad sub-genus of competing antibodies. The relatively narrow sub-genus of competing antibodies and the species are narrower than the disputed sub-genus. Again the facts in the instant matter are far more like those in *Ex parte Sorenson*, where support was found. Here there are four representative species, all of which are within the disputed sub-genus, wherein in *In re Lukach*, where support was not found, there was only one. And again, the facts are even stronger here than in *Ex parte Sorenson*, by virtue of the disclosure of the relatively narrower sub-genus of competing antibodies.

In *Ex parte Lukach*, the court relied very heavily on the lack of other disclosure pointing to the questioned sub-genus in reaching its finding of no support for the questioned sub-genus. Such guiding disclosure is referred to in some cases as blaze marks.[23, 24]

---

[19] See page 19, lines 1-3, of the specification.
[20] See page 35, lines44-46, of the specification.
[21] See page 3, first full paragraph,, of the Final Office Action of November 3, 2004.
[22] All of the disclosed antibodies not only define the scope of the claim (by specifying what an antibody must compete with to be within the claim) but are also within the disputed sub-genus. The fact that use of any one of the specified antibodies would infringe the claim shows they are all within the disputed sub-genus.
[23] The case law has recognized the importance of blaze marks or other disclosure which reasonably leads to the species or genus in question in determining if there is implicit support for a species or genus (in this case sub-genus), see e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 39 USPQ2d 1895 (Fed. Cir. 1996 In re Ruschig, 379 F.2d 990, 994-95, 154 USPQ 118 (CCPA 1967).

There is a wealth of guiding disclosure in the specification pointing to the disputed sub-genus. The amount of guiding disclosure found in the instant specification stands in stark contrast to what was found in *Ex parte Lukach*, where the court failed to find support. In the instant specification, it is clear that sub-genera of competing antibodies of varying scope were disclosed (the relatively broad sub-genus of competing antibodies and the relatively narrow sub-genus of competing antibodies). These sub-genera of competing antibodies point the way to genera of competing antibodies of differing scope. Furthermore, the narrower sub-genus of competing antibodies (which is limited to J591, J533, and E99) points to the use of working examples disclosed in the specification to define the scope of a sub-genus of competing antibodies. The specification describes four, and only four, working examples, J591, E99, J415 and J533. This points the way to this important set of antibodies for use in defining the scope of the disputed sub-genus. There are no species one is forced to overlook or exclude. The guidance so critically lacking in *Ex parte Lukach* is found in the instant specification. The guidance found in the specification points clearly to a sub-genus of competing antibodies limited by being competitive with one of the four sole disclosed species, in other words, the disputed sub-genus.

Thus, the specification reasonably conveys that the inventor was in possession of a sub-genus of competing antibodies defined by these four important species, i.e., the disputed sub-genus, an anti-PSMA antibody which competes with any one of J591, E99, J415 and J533. Accordingly, even if there was no explicit support for the disputed claim term the specification provides implicit support for it.

Written description of a genus, whether support in the disclosure is *in haec verba*, explicit or implicit, also requires disclosure of a sufficient number of species. The Patent and Trademark Office's Revised Interim Written Description Guidelines Training Materials allows a single prophetic example of an antibody to support a genus where the antigen is well characterized. Here there is much more, there are four working examples, the antigen is well characterized, and

---

[24] The arguments in the Final Office Action may be construed to say that the broader sub-genus of competing antibodies is not described in the specification. Appellant's arguments concerning the description of that sub-genus were presented above, under the discussion of explicit support, and are incorporated here as well. The analysis in the Final Office Action is wrong on that count. But even if the broader sub-genus of competing antibodies were not described, the narrower sub-genus of competing antibodies is still there, pointing the way to the disputed sub-genus.

the test for competition is well characterized. The species share structural and functional homology but are representative of the sub-genus, some compete with one another while one does not.

In summary, it is clear that the inventor was in possession of antibodies that compete for binding with E99, J591, J415 or J533. The rejection should be removed the case sent back to the Examiner for immediate allowance.

The brief fee of $500 is enclosed. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: February 15, 2005

Laurie Butler Lawrence
Reg. No. 46,593

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

20989242.doc

Appendix of Claims

68. A method of detecting normal, benign hyperplastic, or cancerous prostate cells in a human subject, comprising:

providing an antibody or antigen binding portion thereof which competes for binding to prostate specific membrane antigen (PSMA) with a monoclonal antibody selected from the group consisting of an E99, a J415, a J533, and a J591 monoclonal antibody, wherein the antibody or antigen binding portion thereof is bound to a label effective to permit detection of normal, benign hyperplastic, or cancerous prostate cells;

administering the antibody or antigen binding portion thereof to the human subject; and

detecting the presence of the normal, benign hyperplastic, or cancerous prostate cells by detecting the label.

69. The method according to claim 68, wherein detecting the label provides an indication of where the prostate cells are localized within the body of the human subject.

70. The method according to claim 69, wherein the label is detected using an imaging device.

71. The method according to claim 68, wherein the administering is carried out parenterally.

72. The method according to claim 68, wherein the administering is carried out intravenously.

73. The method according to claim 68, wherein the administering is carried out by intracavitary instillation.

74. The method according to claim 68, wherein the administering is carried out rectally.

75. The method according to claim 68, wherein the label is detected using a transrectal

probe.

76. The method according to claim 68, wherein the antibody or antigen binding portion thereof is administered following a prostatectomy.

77. The method according to claim 68, wherein the antibody or antigen binding portion thereof is in a composition further comprising a pharmaceutically acceptable carrier, excipient, or stabilizer.

79. The method according to claim 68, wherein the antibody is selected from the group consisting of a monoclonal antibody and a polyclonal antibody.

80. The method according to claim 79, wherein the antibody is a monoclonal antibody selected from the group consisting of an E99, a J415, a J533, and a J591 monoclonal antibody.

81. The method according to claim 79, wherein the antibody is a monoclonal antibody produced by a hybridoma having an ATCC Accession Number selected from the group consisting of HB-12101, HB-12109, HB-12127, and HB-12126.

107. The A method according to claim 68, wherein the prostate cells are prostate epithelial cells.

111. The method according to claim 68, wherein the antibody or antigen binding portion thereof binds to live cells.

116. The method according to claim 68 or 111, wherein the antibody is a monoclonal antibody or the antigen binding portion thereof is derived from a monoclonal antibody.

117. The method according to claim 68 or 111, wherein the antibody or antigen binding portion thereof is internalized with the prostate specific membrane antigen.

118. The method according to claim 68 or 111, wherein the antigen binding portion is selected from the group consisting of a Fab fragment, a $F(ab')_2$ fragment, and a Fv fragment.

119. The method according to claim 68 or 111, wherein the label is selected from the group consisting of a fluorescent label, a biologically-active enzyme label, a radiolabel, a nuclear magnetic resonance active label, a luminescent label, and a chromophore label.

120. The method according to claim 119, wherein the label is a radiolabel.

121. The method according to claim 120, wherein the radiolabel is a short-range radiation emitter.

122. The method according to claim 120, wherein the radiolabel is selected from the group consisting of ^{212}Bi, ^{213}Bi, and ^{211}At.

123. The method according to claim 120, wherein the radiolabel is selected from the group consisting of ^{32}P, ^{125}I, ^{3}H, ^{14}C, and ^{188}Rh.

124. The method according to claim 120, wherein the radiolabel is ^{131}I.

125. The method according to claim 120, wherein the radiolabel is ^{99m}Tc.

126. The method according to claim 120, wherein the radiolabel is ^{111}In.

127. The method according to claim 68, wherein the method is a method of detecting benign hyperplastic cells in the subject.

128. The method according to claim 68, wherein the method is a method of detecting cancerous prostate cells in the subject.

130. The method according to claim 120, wherein the radiolabel is an α-emitter.

131. The method according to claim 120, wherein the radiolabel is a β-emitter.

132. The method according to claim 120, wherein the radiolabel is a γ-emitter.

133. A method of detecting benign hyperplastic prostate cells in a human subject, comprising:

providing an antibody or antigen binding portion thereof which competes for binding to prostate specific membrane antigen (PSMA) with a monoclonal antibody selected from the group consisting of an E99, a J415, a J533, and a J591 monoclonal antibody, wherein the antibody or antigen binding portion thereof is bound to a label effective to permit detection of benign hyperplastic prostate cells;

administering the antibody or antigen binding portion thereof to the human subject; and

detecting the presence of the benign hyperplastic prostate cells by detecting the label.

134. The method according to claim 133, wherein detecting the label provides an indication of where the prostate cells are localized within the body of the human subject.

135. The method according to claim 134, wherein the label is detected using an imaging device.

136. The method according to claim 133, wherein the antibody is a monoclonal antibody selected from the group consisting of an E99, a J415, a J533, and a J591 monoclonal antibody.

137. The method according to claim 133, wherein the antibody or antigen binding portion thereof binds to live cells.

138. The method according to claim 133, wherein the antibody is a monoclonal antibody

or the antigen binding portion thereof is derived from a monoclonal antibody.

139. The method according to claim 133, wherein the antibody or antigen binding portion thereof is internalized with the prostate specific membrane antigen.

140. The method according to claim 133, wherein the label is selected from the group consisting of a fluorescent label, a biologically-active enzyme label, a radiolabel, a nuclear magnetic resonance active label, a luminescent label, and a chromophore label.

141. The method according to claim 140, wherein the label is a radiolabel.

142. The method according to claim 141, wherein the radiolabel is a short-range radiation emitter.

143. A method of detecting cancerous prostate cells in a human subject, comprising:

providing an antibody or antigen binding portion thereof which competes for binding to prostate specific membrane antigen (PSMA) with a monoclonal antibody selected from the group consisting of an E99, a J415, a J533, and a J591 monoclonal antibody, wherein the antibody or antigen binding portion thereof is bound to a label effective to permit detection of cancerous prostate cells;

administering the antibody or antigen binding portion thereof to the human subject; and

detecting the presence of the cancerous prostate cells by detecting the label.

144. The method according to claim 143, wherein detecting the label provides an indication of where the prostate cells are localized within the body of the human subject.

145. The method according to claim 144, wherein the label is detected using an imaging device.

146. The method according to claim 143, wherein the antibody is a monoclonal antibody selected from the group consisting of an E99, a J415, a J533, and a J591 monoclonal antibody.

147. The method according to claim 143, wherein the antibody or antigen binding portion thereof binds to live cells.

148. The method according to claim 143, wherein the antibody is a monoclonal antibody or the antigen binding portion thereof is derived from a monoclonal antibody.

149. The method according to claim 143, wherein the antibody or antigen binding portion thereof is internalized with the prostate specific membrane antigen.

150. The method according to claim 143, wherein the label is selected from the group consisting of a fluorescent label, a biologically-active enzyme label, a radiolabel, a nuclear magnetic resonance active label, a luminescent label, and a chromophore label.

151. The method according to claim 150, wherein the label is a radiolabel.

152. The method according to claim 151, wherein the radiolabel is a short-range radiation emitter.

Evidence Appendix

Attached is the Declaration of Abbie Celniker under 37 CFR 1.132, which was acknowledged and entered by the Examiner in the Final Office Action dated November 3, 2004.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Neil H. Bander
Serial No. : 09/357,709
Filed : July 20, 1999
Title : TREATMENT AND DIAGNOSIS OF PROSTATE CANCER

Art Unit : 1642
Examiner : Gary B. Nickol

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 CFR §1.132

I, Abbie Celniker, Ph.D., pursuant to 37 C.F.R. § 1.132, declare the following:

1. I am currently employed by Millennium Pharmaceuticals, Inc. as Senior Vice President of R&D Strategy and Operations. I am not an inventor on the above-referenced application. My Curriculum Vitae is attached.

2. I have extensive experience in antibody technology. As can be seen from my Curriculum Vitae, I earned a Ph.D. in Molecular Biology in 1986. My doctoral research concerned immunological studies of human cathespin D. I have been involved in the development of antibody-based projects or products in industry since at least 1986. Since at least 1993 I have held senior research and development positions at Millennium Pharmaceuticals, Genetics Institute, Genetics Institute of Wyeth Ayerst Research, and Genentech Inc. All of these positions included oversight of therapeutic and/or diagnostic antibody projects. My experience extends from years before the priority and filing dates of the above-identified application to the present. During this time, I have worked with and/or supervised numerous individuals of ordinary skill in the art of antibody-based technologies and am well acquainted with the qualifications and abilities of one of ordinary skill in this art. At the time the application was filed, 1996, one of ordinary skill in the art would have understood the structure of antibodies, methods of making them, and at least the basics of how the specific binding properties of antibodies could be useful in therapeutic and diagnostic products. Typically, such an individual would have had a Ph.D. in a biological science and some post-doctoral or industry experience.

3. I have reviewed the specification and the pending claims in the above-referenced application. It is my understanding that the pending claims in the above-referenced application include the following language:

> providing an antibody or antigen binding portion thereof which competes for binding to prostate specific membrane antigen (PSMA) with a monoclonal antibody selected from the group consisting of an E99, a J415, a J533, and a J591 monoclonal antibody

As will be described in detail below, upon reviewing the specification of the above-referenced application, one of ordinary skill in the art at the time the application was filed would have believed that the specification discloses, and the inventors were in possession of, this subject matter.

4. It is my understanding that the same or very similar language has been rejected by the Examiner in related cases. All of these related cases have identical specifications. In each case, the rejection was based on the Examiner's argument that the subject matter set out above was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the invention.

5. The reader is directed first to page 27 lines 26-35 of the specification of the above-identified application as filed. This passage discusses a particular embodiment wherein antibodies are used to direct two components[1] to a desired site, and provides as follows:

> ***a first biological agent*** is conjugated with a prodrug which is activated only when in close proximity with a prodrug activator. The prodrug activator is conjugated with ***a second biological agent according to the invention, preferably*** one which binds to a non-competing site on the prostate specific membrane antigen molecule. Whether two biological agents bind to competing or non-competing binding sites can be determined by conventional competitive binding assays. (***emphasis added***).

[1] One component is an inactive drug, or prodrug, and the other is an activator of the prodrug.

From the passage recited above, it is clear to me that the cited text, in combination with the rest of the specification, discloses two types of antibodies[2] --those that compete for binding with an antibody "according to the invention" and those that do not compete for binding with an antibody "according to the invention", the later being preferred in the particular embodiment being described. But whether preferred or not, it is clear from the text that the inventors were in possession of the idea of an antibody which competes for binding with an antibody according to the invention. The text also provides, see, e.g., the last sentence of the quoted passage , what constitutes a competing site and a non-competing site by stating that "whether two biological agents bind to competing or non-competing sites can be determined by conventional competition binding assays." Therefore, the application necessarily discloses the concept of an antibody that competes for binding with an antibody according to the invention. It is clear to me that, upon reviewing the specification of the above-referenced application, one of ordinary skill in the art at the time the application was filed would have believed that the specification discloses and the inventors were in possession of this element of the invention, namely, an antibody that competes for binding with an antibody according to the invention.

6. It is also clear to me that, upon reviewing the specification of the above-referenced application, one of ordinary skill in the art at the time the application was filed would have believed that monoclonal antibodies E99, J415, J533 and J591 are "antibodies according to the invention." These four antibodies are disclosed throughout the application as being antibodies of the invention. In fact, the very next sentence, page 28, lines 1-6, after the passage recited above states as follows:

> For example, monoclonal antibodies J591, J533, and E99 bind to competing binding sites on the prostate specific membrane antigen molecule. Monoclonal antibody J415, on the other hand, binds to a binding site which is non-competing with the site to which J591, J533, and E99 bind.

---

[2] The term "biological agent" is defined at page 16, lines 16-20, to include antibodies. Most of the disclosure in the specification is with regard to antibodies, so one of ordinary skill would undoubtedly view the quoted section as applying to antibodies.

Thus, the application necessarily discloses that monoclonal antibodies E99, J415, J533 and J591 are antibodies according to the invention. Furthermore the specification, in that passage, gives an example of a specific set of antibodies which compete and an antibody that does not compete with members of the group.

7. As indicated in paragraph 5 above, and in particular in the second sentence of the quoted passage, it is clear that the Applicants disclosed a first antibody or portion thereof that competes for binding with a second antibody according to the invention and, as indicated in paragraph 6, monoclonal antibodies E99, J415, J533 and J591 are clearly antibodies according to the invention. It is clear to me –that, upon reviewing the specification of the above-referenced application, one of ordinary skill in the art at the time the application was filed would have believed that the specification discloses and the inventors were in possession of this element of the invention, namely, "antibodies or portions thereof that compete for binding to PSMA with monoclonal antibodies E99, J415, J533 and J591."

8. I want to be clear that I am not saying merely that the text makes it obvious to arrive at "antibodies or portions thereof that compete for binding to PSMA with monoclonal antibodies E99, J415, J533 and J591" or that the specification discloses a general concept of what antibodies might compete and that it is only obvious that these would be E99, J415, J533 and J591. On the contrary, it is clear to me that, upon reviewing the specification of the above-referenced application, one of ordinary skill in the art at the time the application was filed would have believed the text itself describes and actually shows possession of the subject matter in question. It is really a rather simple matter: a series of consecutive sentences in the specification build on one another and require this conclusion. I have summarized the situation below, where the relevant text (e.g., page 27, line 26, through page 28 line 6) is presented in annotated form:

Text from the specification	Meaning
In a particularly preferred embodiment of the present invention, a first biological agent is conjugated with a prodrug which is activated only when in close proximity with a prodrug activator. (page 27, lines 26-29)	
The prodrug activator is conjugated with a second biological agent according to the invention, preferably one which binds to a non-competing site on the prostate specific membrane antigen molecule. Whether two biological agents bind to competing or non-competing binding sites can be determined by conventional competitive binding assays. (page 27, lines 29-35)	These two sentences tell one of ordinary skill that the applicant was in possession of antibodies which compete with antibodies of the invention and give the meaning of the term compete for binding.
For example, monoclonal antibodies J591, J533, and E99 bind to competing binding sites on the prostate specific membrane antigen molecule. Monoclonal antibody J415 on the other hand, binds to a binding site which is non-competing with the site to which J591, J533, and E99 bind. (page 28, lines 1-6)	This sentence, the next sentence in the specification, tells one that the specific antibodies mentioned in the claim (J415, J591, J533 and E99) are antibodies of the invention.

Thus, one reading this passage, learns from the first four sentences that antibodies which compete for binding with antibodies of the invention are described. A few lines later one learns that J415, J591, J533 and E99 are antibodies of the invention. It is simply inescapable that the specific examples of antibodies of the invention, J415, J591, J533 and E99, provided in the text can be placed in the context of the earlier sentence. It is clear to me that, upon reviewing the specification of the above-referenced application, one of ordinary skill in the art at the time the application was filed would have believed

that antibodies that compete for binding with the listed antibodies, in other words, antibodies that compete for binding with one or more of J415, J591, J533 or E99.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

DATE: 7/22/04

Abbie Celniker, Ph.D.

20907000.doc

Abbie C. Celniker, Ph.D.
560 Chestnut Street
Newton, MA 02468
Home: 617-332-0067 Fax: 617-969-7030
Acelniker@AOL.com

Education:

1986, Ph.D., Molecular Biology, University of Arizona. Immunological Studies of Human Cathepsin D

1980, B.A., Biology, University of California, San Diego

Experience Overview:

- Extensive experience in the area of pharmaceutical development and commercialization including; functional line and matrix area oversight.
- Biopharmacetuical Pipeline and Portfolio Management for both small and large molecules
- Specific scientific expertise in the areas of transplantation biology, co-stimulation, growth and wasting.
- Technical expertise in the areas of; monoclonal antibody discovery, development and characterization, immunoassay and analytical methods development and Preclinical biology.
- Managerial experience including the management of individuals and diverse groups consisting of individuals from the VP to RA level.
- Compliance experience including the organization and maintenance of GLP and GMP compliant laboratories and information management systems.
- Translational biology experience focused on the integration of novel analytical methods into clinical studies and the movement of therapeutic proteins from research into the clinic.

Employment:

August 2001 to Present Senior Vice President, R&D Strategy and Operations, **Millennium Pharmaceuticals**, Cambridge, MA. Responsibilities include:

- Oversight the Project Management, Scientific Development and R&D Planning and Operations areas.
- Co-Chair of the Pipeline Review Committee responsible for operational and strategic oversight of the R&D pipeline, investment prioritization and technical review of programs from late lead optimization through commercialization.

- Member of the Strategic Portfolio Committee, a subcommittee of the Management Team responsible for integration of R&D, Commercial, Business Development opportunities.

- Interface with the R&D subcommittee of the BOD on pipeline and R&D strategy.

June 2000 to August 2001 Vice President, Biotherapeutics, **Millennium Pharmaceuticals**, Cambridge, MA. Responsibilities include:

- Oversight of the following functional areas: Therapeutic Antibody Technology Group, Protein Sciences (discovery and process development), Biological Assay Development, Mouse Models Development and the Animal Resources Group.

- Participation on the Discovery Scientific Review Committee, Development Scientific Review Committee and Product Team (development portfolio management)

October 1999 to June 2000, Assistant Vice President, Predevelopment – Biopharmaceutical Core Technologies, **Genetics Institute of Wyeth Ayerst Research**, Andover/Cambridge, MA. Responsibilities included:

- Oversight of the following functional areas: Therapeutic Antibody Technology Group, Research Protein Supply, Proteomics, Bioanalytical Sciences, Pharmacokinetic and Pharmacodynamic Sciences, Laboratory Animal Resources, Preclinical Scientific Communications, Research Operations and the External Research Department.

- Oversight of "predevelopment process" for therapeutic proteins moving from discovery research into development (Lead Candidate through IND).

- Preclinical Project Team Leader for the Anti-B7.1/Anti-B7.2 Program in GvHD and Renal Transplantation

November 1993 to June 1999, Director /Senior Scientist of Bioanalytical Sciences at **Genetics Institute**, Andover, MA. Responsibilities included:

- Oversight of the Antibody Technology Group, Bioanalytical Sciences and the Preclinical Transcriptional Profiling group (Gene Expression Monitoring).

- The establishment and oversight of a GLP compliant immunoassay lab, including laboratory automation (sample tracking, sample manipulation and data transfer), assay validation and facility management.

- Member of the Analytical Coordinating Group (ACG) responsible for the immunoassays used for identity testing, ligand binding analysis and immunoassays for host cell protein impurities to support process and product development.

- Oversight of the assessment and interpretation of anti-product immune responses for Preclinical and clinical studies.

May of 1993 to November 1993, Associate Director/Senior Scientist, Medicinal and Analytical Chemistry, **Genentech Inc.**, South San Francisco, CA. Responsibilities included:

- Oversight of the Bioanalytical Methods Development group, responsible for immunoassay development for research, Preclinical, clinical and product development support

- Preclinical Research Project Team Leader for the IGF-1 Program

June 1986 to May of 1993, Scientist, Medicinal and Analytical Chemistry, **Genentech Inc.**, South San Francisco, CA. Responsibilities included:

- Development of antibodies and immunoassays for the quantitation of human and animal growth hormones in serum and urine and the assessment of the anti-growth hormone antibody response.

- Development of antibodies and immunoassays for the quantitation of human Insulin-like Growth Factor 1 (IGF-1) and IGF-1 binding proteins in serum and urine to support preclinical and clinical pharmcokinetics and pharmacodynamics

- Development of antibodies and immunoassays for the quantitation of gamma interferon, TNF-alpha, HSA, Human Relaxin, Pro-Relaxin, and Relaxin "A" and "B" chains in serum, urine and cell expression systems

- Development of immunoassays for the quantitation of E. coli and CHO derived host cell protein impurities

1984 to 1986, Research Associate, **University of Arizona Cancer Center**, Veteran's Administration Hospital, Tucson, AZ. Responsibilities included:

- Establishment of primary cells lines from prostate tumor and benign prostatic hypertrophy specimens.

- Development of assays to differentiate cytostatic from cytotoxic biological response modifiers.

- Development of immunohistochemical staining methods for the detection of prostate cancer cells in bone marrow.

Publications:

Takai DK, Craighead, N, Saini, A, **Celniker, A.**, Burkly, L.C., Lee, K.P., Chute, J.P., Harlan, D.M. and Kirk, A.D. Costimulatory molecules are active in the human xenoreactive T-cell response but

not in natural killer-mediated cytotoxicity. Transplantation. 2000 Jul 15;70(1):162-7.

Modi, N., Baughman, S., Paasch, B., **Celniker, A.**, and Smith, S. Pharmacokinetics and pharmacodynamics of TP-9201, a GPIIbIIIa antagonist, in rats and dogs. J Cardiovasc Pharmacol. 1995 Jun; 25(6): 888-97.

Boguniewicz, M., Martin, R., Martin, D., Gibson, U., **Celniker, A.**, Williams, M., and Leung, D. The effects of nebulized recombinant interferon-gamma in asthmatic airways. J Allergy Clin Immunol. 1995 Jan;95(1 Pt 1):133-5

Martin, R., Boguniewicz, M., Hensen, J.E., **Celniker, A.**, Williams, M., Giorno, R., and Leung, D.Y. The Safety and Effects of Inhaled Interferon Gamma in Normal Human Airways. Am Rev of Resp Dis 148: 1677-1682, 1993.

Hartman, M.L., Clayton, P.E., Johnson M.L. Perlman, A.J., **Celniker, A.C.**, Alberti, K.G.M.M. and Thorner, M.O. A Low-Dose Euglycemic Infusion of Recombinant Human Insulin-Like Growth Factor I Rapidly Suppresses Fasting-Enhanced Pulsatile Growth Hormone Secretion in Humans. JCI 91: 2453-2462, 1993.

Stewart, D.R., Overstreet, J.W., **Celniker, A.C.**, Hess, D.L., Cragun, J.R., Boyers, S.P. and Lasley, B.L. The Relationship Between HCG and Relaxin Secretion in Normal Pregnancies vs Periimplantation Spontaneous Abortions. Clin Endo 38: 379-385, 1993.

Simon, C.J.Y., Underwood, L.E., **Celniker, A.** and Clemmons, D.R. 1992. Effects of Recombinant Insulin-Like Growth Factor-I (IGF-I) and Growth Hormone on Serum IGF-Binding Proteins in Calorically Restricted Adults. J. Clin Endocrinol. Metab. 75: 603-608, 1992

Lieberman, SA, Bukar, J, Chen, SA, **Celniker, AC**, Compton, PG, Cook, J, Albu, J, Perlman, AJ, and Hoffman, AR. 1992. Effects of Recombinant Human Insulin-Like Growth Factor-I (rhIGF-I) on Total and Free IGF-I Concentrations, IGF Binding Proteins, and Glycemic Response in Humans. J. Clin Endocrinol Metab. 75: 30-36, 1992.

Albini, C.H., Sotos, J., Sherman, B., Johanson, A., **Celniker, A.**, Hopwood, N., Quattrin, T., Mills, B., and MacGillivray, M.H. 1991. Diagnostic Significance of Urinary Growth Hormone Measurements in Children with Growth Failure: correlation between serum and urine GH. Pediatric Research 29: 619-622, 1991.

Ferraiolo, B.L., Winslow, J., Laramee, G., **Celniker, A** and Paul Johnston. The Pharmacokinetics and Metabolism of Human Relaxins in Rhesus Monkeys. Pharmaceutical Research, 8: 1032-1038, 1991.

Girard, J., **Celniker, A.**, Price, A., Tanaka, T., Walker, J., Welling, K., and Albertsson-Wikland, K. Urinary Measurement of Growth Hormone Secretion. Acta Paediatr Scad [Suppl], 366: 149-154, 1990.

Stewart, D.R., **Celniker, A.C.**, Taylor, C.A., Gragun, J.R., Overstreet, J.W. and Lasley. B.L. Relaxin in the Peri-Implantation Period. J. Clin Endocrinol and Met, 70: 1771, 1990

Celniker A.C., Chen, A.B., Wert, R.M. and Sherman, B.M. Variability in the Quantitation of Circulation Growth Hormone Using Commercial Immunoassays. J. Clin Endocrinol and Met, 68: 469, 1989

Ahmann, R.R., Garewal, H.S., Schifman, R., **Celniker, A.** and Rodney, S. Intracellular Adenosine Triphosphate as a Measure of Human Tumor Cell Viability and Drug Modulated Growth. J. In Vitro Cell Dev Biol 23: 474, 1987

Montgomery, D.W., **Celniker, A.** and Zukoski, C.F. Didemnin B--An Immunosupressive Cyclic Peptide that Stimulates Murine Hemagglutinating Antibody Responses and Induces Leukocytosis In Vivo. Transplantation 43: 133, 1987

Nagle, R.B., Ahmann, F.R., McDaniel, K.M., Paquin, M.L., Clark, V.A. and **Celniker, A.** Cytokeratin Characterization of Human Prostatic Carcinoma and Its Derived Cell Lines. Cancer Res 47: 281, 1987

Garewal, H.S., Ahmann, F.R., Schifman, R.B. and **Celniker, A.** ATP Assay: Ability to Distinguish Cytostatic from Cytocidal Anticancer Drug Effects. JNCI 77: 1039, 1986